Docket No.: NEB-164-PUS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Noren et al. EXAMINER: Lundgren

SERIAL NO.: 09/937,187 ART UNIT: 1639

DATE FILED: September 9, 2001

TITLE: Surface Display of Selenocysteine-Containing Peptides

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

I hereby declare that:

1. My name is Dr. Christopher J. Noren, Head of the Bioorganic Chemistry Division at New England Biolabs, Inc., assignee for the above-referenced patent application.

2. The biosynthetic machinery required to synthesize host cell surface proteins and surface (coat) proteins of viruses that are obligate parasites of those cells is the same. Surface proteins are known for both viruses and cells. For example, M13 coat protein pIII is a viral protein while flagella protein is a bacterial host protein. Each of these types of proteins can be genetically fused to a selenocysteine expression cassette which we developed, and the mRNA encoding this is shown in Figure 4 of the above application. The selenocysteine expression cassette that we developed contains a peptide-encoding sequence with an embedded UGA codon,

followed by a SECIS element at a fixed distance from the UGA codon. This construction enables the random peptide library expressed on the surface of a particle (virus or cell) to contain a selenocysteine, thereby providing a unique chemical handle for specific modifications of each displayed peptide in the library.

3. The idea of expressing a random peptide library on the surface of a cell or virion is to provide an affinity-selectable functionality (e.g., a displayed peptide) on the surface of the amplifiable genetic particle (cell or virion), which in turn contains nucleic acid encoding this functionality. Following affinity selection of particles displaying a particular peptide sequence, the particle can be amplified (i.e., grown) and the nucleic acid encoding the individual selected peptide can be recovered and sequenced. While display of random peptide libraries on the surface of a genetically-amplifiable particles (cells and virions) is well known in the art, our inventive claimed contribution is to incorporate a selenocysteine residue into the random peptide library on the surface of the genetic particle. Previous studies on selenocysteine and its mechanism of incorporation have never been applied to random peptide libraries, or to surface display on cells or virions.

4. I further declare that my colleague, Jack Benner, who is named on the Abstract identified by the Examiner from the FASEB meeting published April 23, 1999, vol 13, manages the protein sequencing facility at New England Biolabs Inc. and provided us with protein sequence data at our request. As such he is not an inventor of the present claimed invention.

5. I further declare under penalty of perjury pursuant to laws of the United States of America that the foregoing is true and correct and that the

Declaration was executed by me on:

Dr. Christopher J. Noren Date: June 11, 2006

Christopher J. Noren, Ph.D.

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Professional

2005-present	Head, Division of Bioorganic Chemistry New England Biolabs, Ipswich, MA
2001-present	Instructor Cold Spring Harbor Laboratory, NY Annual two-week course, "Phage Display of Antibodies and Peptides."
1993-2005	Senior Scientist New England Biolabs, Beverly, MA
1990-1993	Staff Scientist New England Biolabs, Beverly, MA

Education

1990	Ph.D. (Chemistry)	University of California, Berkeley Thesis Advisor: Peter G. Schultz Thesis Title: "Site-Specific Mutagenesis with Unnatural Amino Acids"
1984	B.S. (Chemistry)	Massachusetts Institute of Technology Cambridge, MA

Publications

1. **Christopher J. Noren**, Spencer J. Anthony-Cahill, Michael C. Griffith and Peter G. Schultz (1989) "A General Method for Site-Specific Incorporation of Unnatural Amino Acids into Proteins" *Science*, **244**, 182-188.

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3. Stephanie A. Robertson, **Christopher J. Noren**, Spencer J. Anthony-Cahill, Michael C. Griffith and Peter G. Schultz (1989) "The Use of 5'-Phospho-2'-deoxyribocytidylyl-riboadenosine as a Facile Route to Chemical Aminoacylation of tRNA" *Nucleic Acids Res.* **17**, 9649-9660.

4. **Christopher J. Noren,** Spencer J. Anthony-Cahill, Daniel J. Suich, Karen A. Noren, Michael C. Griffith and Peter G. Schultz (1990) "*In Vitro* Suppression of an Amber Mutation by a Chemically Aminoacylated Transfer RNA Prepared by Runoff Transcription" *Nucleic Acids Res.* **18**, 83-88.

5. Jon Ellman, David Mendel, Spencer Anthony-Cahill, **Christopher J. Noren** and Peter G. Schultz (1991) "Biosynthetic Method for Introducing Unnatural Amino Acids Site-Specifically into Proteins" *Methods Enzymol.* **202**, 301-336.

6. Robert A. Hodges, Francine B. Perler, **Christopher J. Noren** and William E. Jack (1992) "Protein Splicing Removes Intervening Sequences in an Archea DNA Polymerase" *Nucleic Acids Res.* **20**, 6153-6157.

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12. Francine B. Perler, Ming-qun Xu, and **Christopher J. Noren** (1997) "Protein Splicing" In: *The Encyclopedia of Molecular Biology*, ed. Creighton, T. E. (John Wiley and Sons, New York).

13. Michael B. Zwick, Lori L.C. Bonnycastle, Karen A. Noren, Sara Venturini, Edward Leong, Carlos F. Barbas, III, **Christopher J. Noren** and Jamie K. Scott (1998) "The Maltose Binding Protein as a Scaffold for Monovalent Display of Peptides Derived from Phage Display Libraries" *Anal Biochem.* **264**, 87-97.

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Patents

1. **Christopher J. Noren** and Paul D. Evans (1997) "Bidirectional *in vitro* Transcription Vectors Utilizing a Single RNA Polymerase for Both Directions" **US #5,691,140.**

2. Donald G. Comb, Francine B. Perler, William E. Jack, Ming-Qun Xu, Robert A. Hodges, **Christopher J. Noren**, Shaorong S. C. Chong, Eric Adam and Maurice Southworth (1998) "Modified Proteins Comprising Controllable Intervening Protein Sequences or their Elements, Methods of Producing Same, and Methods for Purification of a Target Protein Comprised by a Modified Protein" **US #5,834,247.**

3. Richard J. Roberts, Devon R. Byrd, Richard D. Morgan, Jay Patti and **Christopher J. Noren** (2002) "Method for Screening Restriction Endonucleases" **US #6,383,770; #6,689,573; #6,905,837.**

4. **Christopher J. Noren**, Karen E. Sandman and Beth M. Paschal, "Surface Display of Selenocysteine-Containing Peptides" **pending, application #20050048548.**

5. George Tzertzinis, George R. Feehery, Corinna D. Tuckey, **Christopher J. Noren** and Larry A. McReynolds, "Methods and Compositions Relating to Gene Silencing" **pending, application # 20040038278.**

All: 1 Review: 0

1: Biotechnology (N Y). 1995 Apr;13(4):366-72. Related Articles, Links

Expression of thioredoxin random peptide libraries on the Escherichia coli cell surface as functional fusions to flagellin: a system designed for exploring protein-protein interactions.

Lu Z, Murray KS, Van Cleave V, LaVallie ER, Stabl ML, McCoy JM.

Genetics Institute, Inc, Cambridge, MA 02140, USA.

We have developed a system for probing protein/protein interactions which makes use of the bacterial flagellum to display random peptide libraries on the surface of E. coli. In developing the system the entire coding sequence of E. coli thioredoxin (trxA) was inserted into a dispensable region of the gene for flagellin (fliC), the major structural component of the E. coli flagellum. The resulting fusion protein (FLITRX) was efficiently exported and assembled into partially functional flagella on the bacterial cell surface. A diverse library of random dodecapeptides were displayed in FLITRX on the exterior of E. coli as conformationally constrained insertions into the thioredoxin active-site loop, a location known to be a highly permissive site for the insertion of exogenous peptide sequences into native thioredoxin. To demonstrate that members of this library could be bound and selected via specific protein/protein interactions to a target protein, a method was devised to enable efficient isolation of those bacteria displaying peptides with affinity to immobilized antibodies. We have unambiguously mapped three different antibody epitopes using this method. Peptides selected as FLITRX active-site fusions retain their binding specificity when made as native thioredoxin active-site loop fusions. This will facilitate future structural characterizations and broaden the general utility of the system for exploring other classes of protein-protein interactions.

PMID: 9634778 [PubMed - indexed for MEDLINE]

Jul 6 2006 07:09:19

Docket No. : NEB-164-PCIP-US Title : Surface Display of
Inventor : Noren et al. Selenocysteine-Containing
Filed : 7/16/2004 Peptides
Serial No. : 10/893,744

The following documents are being deposited with the US Postal Service in an envelope addressed to the Commissioner for Patents on July 11, 2006:

Response to restriction and Transmittal for same; Petition for 1 month extension of time; $60 check

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Practitioner's Docket No. NEB-164-PCIP-US *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Christopher Noren, Karen E. Sandman and Beth Martell Paschal

Application No.: 10/893,744 Group No.: 1639
Filed: 07/16/2004 Examiner: Steele
For: Surface Display of Selenocysteine-Containing Peptides

Mail Stop Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT TRANSMITTAL

1. Transmitted herewith is an amendment for this application.

STATUS

2. Applicant is a small entity. A statement was already filed.

EXTENSION OF TERM

3. The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136 apply. Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(4)) for one month:

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*
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I hereby certify that, on the date shown below, this correspondence is being:

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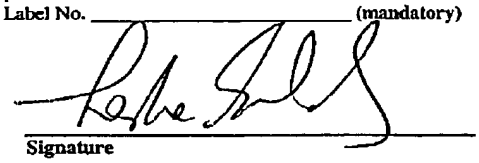

Signature

Date: July 11, 2006

Leslie Goldberg

(type or print name of person certifying)

* *Only the date of filing (' 1.6) will be the date used in a patent term adjustment calculation, although the date on any certificate of mailing or transmission under ' 1.8 continues to be taken into account in determining timeliness. See ' 1.703(f). Consider "Express Mail Post Office to Addressee" (' 1.10) or facsimile transmission (' 1.6(d)) for the reply to be accorded the earliest possible filing date for patent term adjustment calculations.*

Fee: $60.00

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. 1.16(b)-(d)) has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR		(Col. 3) PRESENT EXTRA		SMALL ENTITY RATE		ADDIT. FEE
TOTAL	29	–	29	=	0	x	$ 25.00	=	$ 0.00
INDEP.	5	–	5	=	0	x	$ 100.00	=	$ 0.00
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM						+	$ 0.00	=	$ 0.00
							TOTAL ADDIT. FEE		$ 0.00

No additional fee for claims is required.

FEE PAYMENT

5. Attached is a check in the sum of $60.00.

A duplicate of this paper is attached.

FEE DEFICIENCY

6. If an additional extension and/or fee is required, charge Account No. 14-0740.

If an additional fee for claims is required, charge Account No. 14-0740.

Date: July 11, 2006

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Docket: NEB-164-PCIP-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Sandman et al.	EXAMINER:	Steele
SERIAL NO.:	10/893,744	GROUP:	1639
FILED:	July 16, 2004		
FOR:	Surface Display of Selenocysteine-Containing Peptides		

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Leslie Goldberg

Sir:

AMENDMENT

In response to the Office Action dated June 1, 2006, Applicants elect Group IV, claim 27 without traverse. A listing of the claims begins on page 2 of this paper. The Conclusion section appears on page 7.

WHAT IS CLAIMED IS:

1. (withdrawn) An amplifiable genetic particle, comprising:
a surface containing a protein to which one or more recombinantly expressed peptides are covalently linked wherein each peptide has one or more selenocysteines located at a specific and unique site.

2. (withdrawn) An amplifiable genetic particle of claim 1, wherein the covalent linkage between the selenocysteine containing peptide and the surface protein comprises a native peptide bond.

3. (withdrawn) The particle according to claim 1, wherein the peptide is expressed by a DNA having a TGA codon and a part or all of a selenocysteine insertion sequence.

4. (withdrawn) The particle according to claim 3, wherein the selenocysteine insertion sequence begins one or more nucleotides from the TGA codon.

5. (withdrawn) The particle according to claim 1, selected from a phage, a polysome, a virus, a cell or a spore.

6. (withdrawn) The particle according to claim 1, wherein the displayed selenocysteine residue is flanked on either or both sides by one or more randomized amino acids.

7. (withdrawn) The particle according to claim 1, further comprising one or more randomized amino acid residues flanked by a cysteine residue on one side and a selenocysteine residue on the other side.

8. (withdrawn) The particle according to claim 4, wherein the selenocysteine insertion sequence is obtained from the group consisting of eubacteria, eukarya and archaea.

9. (withdrawn) The particle according to claim 1, wherein the selenocysteine is capable of chemical derivatization of the selenol group.

10. (withdrawn) The particle according to claim 9, wherein the chemical derivatization results from a nucleophilic substitution reaction.

11. (withdrawn) The particle according to claim 9, wherein the chemical derivatization results from an oxidation reaction.

12. (withdrawn) The particle according to claim 9, wherein the chemical derivatization results from a metal coordination reaction.

13. (withdrawn) The particle according to claim 9, wherein the selenocysteine is chemically derivatized with a chemical functionality selected from the group consisting of enzyme substrates, enzyme cofactors, enzyme inhibitors, receptor ligands and cytotoxic agents.

14. (withdrawn) The particle according to claims 1 or 10 wherein the one or more peptides further comprise at least one peptide that forms an enzyme substrate or is modified at the selenocysteine to form an enzyme substrate, the amplifiable genetic particle further comprising a recombinantly expressed enzyme on the surface of the amplifiable genetic particle.

15. (withdrawn) The particle according to claim 14, wherein the reaction product of the enzyme and the enzyme substrate is located on the surface of the amplifiable genetic particle.

16. (withdrawn) The particle of claim 14, wherein the reaction product is capable of binding to an affinity substrate.

17. (withdrawn) The particle according to claim 14, wherein the recombinantly expressed enzyme is selected from a library of variants of a single enzyme, wherein each variant contains one or more amino acid substitutions relative to the native enzyme.

18. (withdrawn) The particle according to claim 14, wherein the recombinantly expressed enzyme is obtained from an expressed cDNA library.

19. (withdrawn) The particle according to claim 13, wherein the chemical functionality is a known ligand for a target protein.

20. (withdrawn) The particle according to claim 19, wherein the target protein is an enzyme and the ligand is an enzyme inhibitor or substrate.

21. (withdrawn) The particle according to claim 1, wherein the recombinantly expressed protein containing a selenocysteine is fused to a ligand via the selenocysteine, the fused ligand having improved binding activity compared to the non-fused ligand.

22. (withdrawn) A fusion protein, comprising: a recombinantly expressed protein containing one or more selenocysteines at a predetermined site in the protein, wherein the recombinantly expressed protein is fused to a known ligand for a target molecule.

23. (withdrawn) A fusion protein according to claim 22, wherein the target molecule is an enzyme and the ligand is an enzyme inhibitor or substrate.

24. (withdrawn) A fusion protein, according to claim 22, wherein the recombinantly expressed protein fused to the ligand has improved binding activity to the target protein compared to the non-fused ligand.

25. (withdrawn) A method of screening for peptide-ligand fusion molecules having improved binding to a target molecule compared to non-fused ligand, comprising:

(a) reacting chemically derivatized selenocysteine residues in a random peptide library with a ligand to form a chemically modified peptide library, the chemically modified peptide library being displayed on the surface of an amplifiable particle;

(b) allowing the chemically modified peptide library to bind to the target molecule, wherein the target molecule is immobilized before or after binding to the peptide library;

(c) removing unbound particles;

(d) eluting bound particles; and

(e) identifying peptide-ligand fusion molecules from step (d) with improved binding to the target molecules.

26. (withdrawn) The method according to claim 25, wherein the target protein is an enzyme and the ligand is an enzyme inhibitor.

27. (original) A method of identifying required DNA sequence elements for incorporation of selenocysteine into peptides comprising the steps of:

(a) fusing a selenocysteine expression cassette to a surface peptide of an amplifiable genetic particle, whereby expression of the surface peptide is dependent upon incorporating a selenocysteine residue;

(b) forming a library of sequence variants of the selenocysteine expression cassette; and

(c) selecting for particles which are genetically amplifiable.

28. (withdrawn) A method for discovery of structurally constrained ligands for a target molecule comprising the following steps:

(a) reacting a structurally constrained peptide library displayed on the surface of an amplifiable genetic particle, comprising one or more randomized amino acid residues flanked by a cysteine residue on one side and a selenocysteine residue on the other side, with a target molecule to form bound particles;

(b) removing unbound particles;

(c) eluting bound particles; and

(d) identifying peptide sequence displayed on the eluted bound particles.

CONCLUSION

Applicants have elected Group IV, claim 27.

For the reasons set forth above, Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited. Applicants petition for a one-month extension of time and enclose check in the amount of $60. Please charge any deficiencies to Deposit Account No. 14-0740.

Respectfully submitted,

NEW ENGLAND BIOLABS, INC.

Date: July 11, 2006

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